REMARKS

Claims 85-92 and 107-118 are pending after the entry of this amendment. Claims 93-106 have been cancelled. This is not a surrender of subject matter and Applicants reserve the right to pursue the subject matter at a later point in time. Claims 85, 90, 107, and 109-111 have been amended. Claims 116-118 have been added. Support for these amendments and new claims can be found in the original claims and throughout the specification, for example Figures 1-3, Claim 7 and paragraphs 9-32, 60-62, 110-119, and 140-150. No new matter has been added by these amendments or new claims.

Applicants thank the Examiner for withdrawing the species requirements in regard to species I, II, and III.

Applicants thank the Examiner for the withdrawal of the previous objection to the specification and the withdrawal of the rejections under 35 USC §112 (new matter), 35 USC §101 (for claims 85-92), 35 USC §112 (enablement), and 35 USC §102(b) (both Yaffe and Mamitsuka).

Claims 85-92, 114, and 115 are adequately definite.

The Examiner has rejected independent Claims 85 and 90 as allegedly being indefinite because of the use of the term "product" in the claim. While the Applicants do not necessarily agree with this rejection, Claims 85 and 90 have been amended to replace the term "product" with "result" to clarify the term for the Examiner. Applicants note that the term refers to one of the results from the various steps in the method (e.g., the first or second predicted affinity, the scaled values, the combined scaled values, etc.). As such, Applicants respectfully submit that the claims are now sufficiently definite and request that the rejection be withdrawn and the claims allowed. Applicants note that the amendments do not narrow the claims.

Claims 107-111 are statutory under 35 U.S.C. §101.

The Examiner has asserted that Claims 107-111 are directed to nonstatutory subject matter. Independent Claim 107 has been amended to recite, "outputting a result from the above steps," as recommended by the Examiner. As such, Applicants submit that the claimed subject matter is statutory.

Applicants note that Claims 109, 110, and 111 previously included an outputting step (and now recite outputting a "result") and thus should be statutory for the reasons set forth by the Examiner. Applicants assume that the presence of these elements in Claims 109, 110, and 111 may have simply been overlooked (as they were not addressed in the previous Office Action). However, if the Examiner has a specific issue with these particular elements, Applicants request that the reasons be made of record so that Applicants can address any concerns the Examiner may have on the record.

Claims 85-92 and 109-115 are nonobvious over the combination of Rognan and Yaffe.

The Examiner has asserted that Claims 85-92 and 109-115 are obvious over Rognan et al. (hereinafter "Rogan") in light of Yaffe et al. (hereinafter "Yaffe"). In making the rejection, the Examiner has asserted the following:

1. The "scores" discussed in Yaffe can be interpreted as "affinities," as recited in the present claims and as used in the present application.
2. Rognan et al. teaches five distinct methods of predictive scoring to determine an overall predictive score.
3. "Yaffe et al. teach a profile-based method for predicting protein-protein interactions [Abstract], as set forth in the previous office action mailed 02/01/2007. More specifically, Yaffe et al. teach the following aspects of the instant claims:
    - Obtaining known peptide sequence data and surface accessibility values (i.e. binding information) [p. 353, Col. 1, ¶ 3], as in claim 85, 90....
    - Profile-based scoring algorithm comprising bit scores (i.e. first affinity) calculated for putative motifs domains using a first equation (i.e. first predictive method) [p.349, Col. 1, ¶ 1] that employs sequence information from experimental data [p.353. Col. 1, ¶ 3], as in claims 85, 89, and 92.
    - Profile-based scoring algorithm also comprising raw sequence scores (i.e. second affinity) calculated using a second equation [p.349, Col. 1, 11 1] and [Fig. 3] that employs and compares sequence information from putative motifs and experimental data [p.353, Col. 1, ¶ 3], as in claims 85, 90.
    - Normalizing (i.e. scaling) bit scores and raw sequence scores [p.349, Col. 1, ¶ 1], which inherently results in values between 0 and 1, as in claims 85, 87, 90.

- Combining normalized raw scores and optimal scores to calculate a final sequence score (S_f), wherein final sequence score is used for assessing the affinity between putative motifs and a target sequence [p. 349, Col.1, ¶ 1] as in claim 85." (Final Office Action, page 8).

Applicants respectfully traverse the rejection and disagree with the Examiner's assertions recited above.

Yaffe's Scores are not a Measure of Affinity

In regard to the first point (1.) above, the "scores" in Yaffe are clearly distinct from the "affinities" recited in the present claims. Yaffe is directed to techniques for predicting signaling pathways within entire genomes (*see*, entire paper, *e.g.*, title and abstract). The basic idea behind the approach is to use motif-based profile scanning to match, in a single protein, multiple different domains that are present in a common signaling pathway. Yaffe suggests that this would mean that the protein in question is likely part of that signaling pathway.

Applicants note that, at best, Yaffe's "scores" might be interpreted as a measure of how well a sequence matches a particular motif; however, this is not the same thing as providing an actual prediction or determination of an affinity of a target protein to a candidate peptide. As explicitly recited in the specification, the term "binding affinity" refers "to the likelihood that a peptide would associate with a protein." (¶ 0130). In contrast, the term "score" in Yaffe is used to denote the "quality of the match" between a motif and a motif profile for predicting whether a protein should be incorporated into a signaling pathway (p. 348, col. 2, 3rd ¶). Thus, the "score" for Yaffe is only indicative of the match between a sequence and a given motif, the score itself need not be indicative of the likelihood of binding occurring between a protein and a candidate protein, as is required for the presently recited term affinity. As Yaffe's score is not the same as the term "affinity" recited in the present claims, the reference does not teach all of the elements of the claimed invention and does not make up for deficiencies of the primary reference.

Rognan's Approaches Cannot be Characterized as a First and a Second Method

In regard to the second point above (2.), the relationship of the recited claim elements prevents the five aspects described in Rognan from being interpreted as five different methods, as suggested in the Examiner's rejection. In particular, in the claimed invention the first and second predictions are determined using separate methods. After each affinity is separately determined,

the two affinities are then scaled and then combined. In contrast, the cited teachings in Rognan are all factors involved in obtaining a single affinity and, more importantly, none of these are disclosed as being scaled as recited in the claims prior to their combination. As such, neither Rognan nor Yaffe teach combining affinity values that have been derived from different techniques, scaling these values (as recited in the claims), and then combining these scaled values. As such, not all of the claimed elements have been taught by the cited art.

Yaffe does not Teach Determining a First Affinity and a Second Affinity

In regard to the third point above (3.), Applicants note that the cited sections of Yaffe do not teach the elements of the claims as the Examiner suggested in the Office Action.

In contrast to what is asserted by the Examiner, the "surface accessibility value" is not the same as the recited affinity values. The affinity values recited in the claims are between the candidate peptide and the protein. In contrast, the surface accessibility value (discussed in ¶ 1, col. 2, p. 349 of Yaffe) is simply a prediction of which amino acids are on the surface of the protein. As such, this section of Yaffe does not teach a way to obtain relevant binding information.

Additionally, Applicants note that, in contrast to the Examiner's proposal that "bit scores" and "raw scores" serve as first and second affinities, it is clear from Yaffe that these values cannot be first and second affinities between a candidate peptide and a target protein. In col. 1, ¶ 1 of page 349 of Yaffe explicitly defines the bit score as:

$$\ln(\chi_i)/\ln 2$$

and the raw score as:

$$\Sigma[\mathbf{\ln(\chi_i)/\ln 2}]/i$$

Thus, Yaffe's explicitly recited definition of the two terms excludes the Examiner's interpretation, as the bit score is used to determine the raw score (shown in bold in the formula of the raw score above). As such, these two scores clearly cannot be interpreted as a first and second affinity which are each determined, then scaled, and then combined with one another.

Furthermore, Applicants note that Yaffe clearly shows that the bit scores alone are not a "first affinity" between a candidate peptide and a target protein as the bit scores are derived for each amino acid (see p. 349, 1st ¶, col. 1). Similarly, it is also clear that the raw selectivity scores

are also different from an affinity value because the raw selectivity values are values provided for specific amino acids and are not values for the candidate peptide for the target protein (page 353, col. 1, ¶ 3). In contrast, the claims clearly recite affinities "for the candidate peptide for said target protein." Thus, the Examiner's interpretation of "score," "bit score," and "raw score" is clearly inconsistent with the actual teachings of Yaffe.

As noted above, the raw scores employ the bit scores in their determination, as such, it is clear that Yaffe cannot teach "normalizing (*i.e.* scaling) bit scores and raw scores..." as suggested by the Examiner (page 6 of the Office Action).

Finally, Yaffe's teaching of an "optimal" score has no relevance as a first or second affinity either as it is simply an ideal score value, and cannot be considered as either a first or second affinity.

As Yaffe does not actually determine a first and second affinity by different methods, much less scale and combine the affinities, a *prima facie* case of obviousness has not been established and Applicants request the rejections be withdrawn and the claims allowed.

Claims 85, 87-90, 92, 109-115 are nonobvious over the combination of Yaffe and Geetha.

The Examiner has asserted that Claims 85, 87-90, 92, and 109-115 are obvious over Yaffe in view of Geetha et al. (hereinafter "Geetha"). In making the rejection, the Examiner has asserted the following:

1. Yaffe compares their recited method to structure-based predictive methods.
2. Geetha provides structure-based predictive methods (i.e. FORESST) for evaluating binding capabilities based on quadratic programming and calculation of Z-scores that determine the affinity of a match between candidate and target proteins, as in claims 85, 90, and 109-113.
3. Geetha teaches that the combination of structure and function methods can be used to improve binding affinity prediction using a model that incorporates sequence and structural predictive methods [Geetha et al., Conclusion].

Applicants respectfully traverse the rejection and disagree with the Examiner's characterization of the art noted above.

Yaffe's "Comparison" to Structure-Based Methods, if Anything, Teaches Away from the Presently Claimed Method.

In regard to the first point (1.), the "comparison" in Yaffe that the Examiner refers to (p. 352, Col. 2, ¶3) is only a comparison to verify their data and is not a suggestion that the various forms of data should or could be combined. Indeed, Yaffe notes that the "level of predictive accuracy for phosphorylation sites is comparable to that for algorithms used to predict protein secondary structure, and is significantly better than that found using a strict pattern recognition approach." If anything, this statement suggests that, of the various techniques discussed, only the best technique should be employed (as the other gives more false leads). This implies that the techniques should each be used separately and that only one would be the correct one to use. Thus, Yaffe, if anything, appears to teach away from the presently claimed methods that combine the results from various techniques and certainly provides no reason for their combination.

Geetha is Nonanalogous Art and Does Not Teach the Determination of Binding Abilities

In regard to the second item note above (2.), Geetha is not directed to technology that involves predicting binding affinity, but is directed to an unrelated issue of "remote homolog identification" (see entire paper, *e.g.*, title, and abstract). This does not appear to have any relationship to predicting binding affinities, but instead relates to the degree of relatedness of proteins on an evolutionary tree. As an initial point, Applicants submit that this issue is so unrelated to the present issue (of predicting affinities between various proteins) that Geetha is nonanalogous art. Apart from the fact it involves prediction techniques and that the subject is biological, there seems to be nothing else associating Geetha (homology prediction) to the technology that is relevant to the claimed methods (predicting protein binding affinities). Applicants submit that as the technologies disclosed in Geetha and the present application do not appear to overlap significantly, that Geetha is nonanalogous art, and cannot be applied in a proper rejection under 35 U.S.C. §103.

However, Applicants note that even if Geetha were considered to be available for obviousness purposes, it still does not teach the propositions noted above and asserted by the Examiner. The Examiner has asserted that Geetha teaches a structure-based predictive method on page 530, col. 2, ¶ 2 and the "calculation of Z-scores that determine the affinity of a match

between candidate and target proteins [p.529, Col. 1, ¶ 2], as in claims 85, 90, and 109-113." However, the discussion on page 530 (col. 2, ¶ 2) only relates to evaluating sequences for homology determination (*e.g.*, to determine how related two proteins are) and the discussion on page 529, Col. 1, ¶ 2 is similarly limited to homology determinations. In contrast to what has been asserted by the Examiner, the cited sections of Geetha (and Geetha in general) do not appear directed to affinity determinations by any stretch of the imagination. As such, Geetha does not actually teach the aspects noted by the Examiner in his rejection or make up for the deficiencies of Yaffe.

Geetha Does Not Teach the Combination of Sequence and Structure Based techniques; but does Teach Away from Such a Combination

In regard to the third point noted above (3.), Applicants note that Geetha's actual conclusion is not that one should combine the two techniques. Rather, Geetha explicitly states in the conclusion the following:

> In choosing between sequence-based or sequence-structure-based methods for fold recognition, one should be guided by the degree of relatedness of the homolog being sought. Our results suggest that a hybrid method utilizing both sequence (for close homolog searches) and secondary structure prediction methods (for remote homolog searches), would be an even better approach...

As is appreciated by one of skill in the art, this statement does not teach that these two approaches should be combined at the same time or for any one sequence. Indeed, it actually teaches away from the combination proposed by the Examiner. In particular, Geetha explicitly teaches that one method (sequence) should be applied for close homolog searches and that a second method (secondary structure) should be applied for remote homolog searches. If anything, this teaches away from a situation in which two approaches are combined, regardless of the degree of homology. Further, Applicants note again that these homology predictions need have nothing to do with affinity determinations.

As Geetha is not applicable to the presently claimed technology, does not teach the recited elements, and, assuming the Examiner finds Geetha relevant, the reference actually teaches away from combining various techniques, Applicants submit that a *prima facie* case of

obviousness has not been established. Applicants request that the rejection be withdrawn and the claims allowed.

Claims 116-118 are nonobvious for additional reasons.

> Claims 116-118 recite the following element:
>
> wherein said first and second affinity are presented in terms selected from the group consisting of relative binding efficiencies, IC-50 values, and categorical binding affinities…

Applicants note that this element is not taught in Yaffe, as Yaffe merely teaches the identification of peptide sections in candidate protein sequences. Yaffe is simply looking for the presence or absence of key motifs to see what other proteins the candidate protein interacts with and how it fits into the pathway. As such, there is no reason for one of skill in the art to present any of the results obtained from the method of Yaffe in terms of "relative binding efficiencies, IC-50 values, and categorical binding affinities." Thus, the above element further distinguishes Claims 116-118 from the cited art.

No Disclaimers or Disavowals

Although the present communication may include alterations to the application or claims, or characterizations of claim scope or referenced art, Applicants are not conceding in this application that previously pending claims are not patentable over the cited references. Rather, any alterations or characterizations are being made to facilitate expeditious prosecution of this application. Applicants reserve the right to pursue at a later date any previously pending or other broader or narrower claims that capture any subject matter supported by the present disclosure, including subject matter found to be specifically disclaimed herein or by any prior prosecution. Accordingly, reviewers of this or any parent, child or related prosecution history shall not reasonably infer that the Applicants have made any disclaimers or disavowals of any subject matter supported by the present application.

CONCLUSION

In view of the foregoing amendments and remarks, Applicants respectfully submit that the pending claims are in condition for allowance and request the same. If, however, some issue

remains that the Examiner feels can be addressed by Examiner Amendment, the Examiner is cordially invited to call the undersigned for authorization.

Please charge any additional fees, including any fees for additional extension of time, or credit overpayment to Deposit Account No. 11-1410.

Respectfully submitted,

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